REMARKS

This Amendment cancels claims 29 and 30 and amends claim 16. The heterocyclic ring-containing organic acid feature of claim 16 is taken from claims 29 and 30. Claims 16, 19-22 and 28 are pending.

A Request for Continued Examination is attached. Entry and favorable consideration of this Amendment, the Declaration Pursuant to 37 C.F.R. § 1.132 and the Supplemental Information Disclosure Statement, are requested.

Examiners Simmons and Fetterolf are thanked for the courtesies extended to Dr. Lasse Leino and the undersigned during the interview held March 10, 2009. The Examiner Interview Summary Record accurately reflects the substance of the interview.

The 35 U.S.C. § 103(a) rejection of claims 16, 19-22 and 28-30 over U.S. Patent No. 5,494,676 to Stab et al. in view of PCT Patent Publication WO 02/07520 to Wei et al. is traversed. The claimed method includes administration of a pharmaceutical composition comprising a pharmaceutically acceptable agent or salt thereof capable of acidifying cell cytoplasm, wherein the pharmaceutically acceptable agent is an organic acid having a heterocyclic ring and a dissociation constant in the range 6.7 to 7.4, and wherein the

agent is mixed with a carrier to adjust the pH of the composition to a range of 6.1 to 7.0. The claimed method specifies an effective amount of the pharmaceutically acceptable agent be administered in non-dissociated form to a person or animal.

The cited combination of references fails to raise a prima facie case of obviousness against the claimed method because one of ordinary skill in the art would not combine the references as suggested by the Patent office.

As a threshold matter, the second step of the Graham test for patentability requires "differences between the prior art and the claims at issue are to be ascertained". KSR Int'l Co. v. Teleflex Inc., 350 U.S. 398, 82 USPQ2d 1385 (2007) reaffirmed the continuing vitality of the Graham test. Accordingly, the Patent Office must consider the differences between Stab et al. and the claimed method, and the differences between Wei et al. and the claimed method.

The pH of Stab et al.'s cream formulation is 4.74, well below the 6.1 to 7.0 pH range of the pharmaceutical composition used in the claimed method. See the Declaration Pursuant to 37 C.F.R. 1.132 by Dr. Jarmo Laihia, filed February 2, 2008. Stab et al. fails to disclose or suggest mixing its pharmaceutically acceptable

agent (cis-urocanic acid) with a carrier to adjust the pH of the composition to a range of 6.1 to 7.0.

Page 4, lines 15-18 of Wei et al. are cited to show motivation to use topical compositions at a pH of from about 5.5 to about 8, which is said to result in less problems with irritation to the skin. Yet Wei et al. provide absolutely no support (e.g. an example or a reference) for their claim that an anti-microbial composition having a pH of from about 5.5 to about 8 will result in less skin irritation.

Those of ordinary skill in the art would discount Wei et al.'s relatively neutral pH claim for the following reasons:

A. Role of acidic, neutral and alkaline pH *per se* in skin irritation

Those of ordinary skill in the art would not believe the pH of a dermatological composition causes skin irritation. Murahata et al., "Effect of pH on the Production of Irritation in a Chamber Irritation Test," 18 J. Am. Acad. Dermatol. 62 (1988), teaches the application of simple buffers adjusted to pH 4.0-10.5 in a standard skin irritation test did not result in clinical skin irritation. See Fig. 2. Similarly, Antoine et al., "pH Influence of Surfactant-induced Skin Irritation," 37 Derm. Beruf. Umwelt. 96 (1989) teaches that "pH cannot be considered as a major

contributive factor of irritancy" in surfactant-induced (sodium lauryl sulfate) skin irritation at a pH range of 5 to 9 (Summary, last paragraph). Berner et al., "The Relationship between pKa and Skin Irritation for Series of Basic Penetrants in Man," 15 Fund. Applied. Toxic. 760 (1990) studied the skin irritation of aqueous solutions of 5 organic compounds with pH values of 7.9 to 11.2 and water solutions with pH values of 6.9, 10.4, and 11.8. Berner et al. found no correlation between the pH of the organic compound solutions and irritation, as measured by skin erythema, edema and redness. Additionally, the high pH water solutions produced no more skin irritation than water at pH 6.9. See page 675, Table 2. Finally, Bucher et al., "Irritant Actions of Unphysiological pH Values. A Controlled Procedure to Test for Topical Irritancy," 9 Agents Actions 124 (1979) teaches that buffer solutions with pH values from 5 to 9 are non-irritant, while more acidic (pH 3-4) or more alkaline buffer solutions (pH 10-11) produced some reactions in an abdominal skin test of juvenile white mice (page 129, Fig. 4).

The applicants conducted extensive tests on human volunteers to investigate the role of pH in skin irritation. See the enclosed Declaration Pursuant to 37 C.F.R. § 1.132, which reports

application of aqueous solutions adjusted to fourteen (14) different pH values between pH 3.5 and pH 10 did not irritate skin in comparison to purified water, measured by visual inspection and by sophisticated instrumentation.

B. Role of pH in skin irritation by a complex mixture of substances

The Patent Office now cites Baranda et al., 41 Int'l J. Dermatology 494 (2002) to support its argument that one of ordinary skill in the art would be motivated to adjust the pH of Stab et al.'s composition from 4.74 to within the range 6.1 to 7.0.

Baranda et al. tested soaps and skin cleansers for skin irritation. The soaps were grouped into three categories based on Barenda et al.'s skin irritation and pH data:

Group I: Low irritation index (IrIn) and pH of 3-8;

Group II: High pH (about pH 10) and high IrIn; and

Group III: Highest pH (about pH 12) and moderate IrIn.

Baranda et al. has an important scientific flaw. As admitted by the authors (page 498, left col., lines 1-2), soaps and skin cleansers contain a complex mixture of substances. For example, Zest Aqua Bar (a soap used in the Barenda et al. study) contains Sodium Tallowate and/or Sodium Palmate, Sodium Cocoate and/or Sodium Palm Kernelate, Water, Fragrance, Aloe Barbadensis Leaf

Extract, Malva Sylvestris Flower Extract, Tocopherol, Glycerin, Sodium Chloride, Coconut Acid, Palm Acid, Palm Kernel Acid, Tallow Acid, Titanium Oxide, EDTA, Green 3, and Yellow.[1] On the other hand, Dove Pink (another soap used in the Barenda et al. study) contains Sodium Lauroyl Isothionate, Stearic Acid, Sodium Tallowate or Sodium Palmitate, Lauric Acid, Sodium Isothionate, Water, Sodium Stearate, Cocoamidopropyl Betaine, Sodium Cocolate or Sodium Palm, Kernelate, Fragrance, Sodium Chloride, EDTA, Tetrasodium Etidronate, Red 17, and Titanium Dioxide.[2] Only about half of the listed ingredients are common for both products. Moreover, these two products, as well as the rest of the tested soaps and skin cleansers, contain complex additives (e.g., colorants, fragrances and plant extracts) which are present in undisclosed quality and quantity.

In short, Baranda et al. tested soaps and skin cleansers which differ from each other in several aspects – not just by pH. Yet Baranda et al. completely ignore the fact that each of the tested product was different in composition and that they may contain

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[1]See http://www.pg.com/company/our_commitment/msds/beauty_care.shtml#8.

[2]See http://dove.msn.com.

substances which are capable of irritating skin even in the absence of alkaline pH.

Baranda et al. fail to demonstrate a causal relationship between pH and skin irritation. Only a test where the composition of the soap or skin cleanser is kept constant over the pH range would demonstrate the role of pH in skin irritation.[3]

Baranda et al. claim[4] to have found a significant correlation between pH and skin irritation. Yet a positive correlation is insufficient to establish a causative relationship between two

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[3]In order to prove alkaline pH is the causative or contributing agent for skin irritation the following experiment should have been performed: Water solutions of a soap or skin cleanser are prepared. The pH of these solutions is adjusted to a pH range 3 to 12 so that representative solutions over the pH range under investigation are made. These solutions are then tested on skin as described in Baranda et al.

[4] Baranda et al.'s correlation is not continuous over their investigated pH range (pH 3-12). Close examination of the data points in Group 1 demonstrates there is no correlation between the pH and skin irritation when the pH is 3-8. More specifically, the applicants determined the Pearson's correlation coefficient for the pH and IrIn values in Group 1. The p-value for correlation was determined after Fisher's Z transformation. No statistically significant correlation was observed. Because there are no data points between pH 8 and 10, it is impossible to make any conclusions at this range. Only when the pH is about 10 (more accurately 9.75), does skin irritation becomes relevant. In short, there is no experimental data in Baranda et al. to conclude skin irritation occurs at pH below 9.75. Thus, one of ordinary skill would not adjust the compositions of Stab et al. to a pH range of 6.1 to 7.0 based on Baranda et al.

phenomena. Consider the following example: the number of HIV infections increased rapidly in 1980's in the U.S. In the same decade, the number of personal computers in occupational and household use also increased markedly. Thus, there is a positive correlation between the number of HIV infections and PCs. However, no one would argue there is a causative link between HIV infection and personal computers.

Those of ordinary skill in the art would ignore Baranda et al. because there is an overwhelming amount of evidence which demonstrates pH has no role in skin irritation, even in complex mixtures of substances. McKinney et al., "Irritant Action of Binary Soaps Mixtures on Skin," Oil & Soap 198 (1940) tested binary mixtures of soap and salt ingredients used in commercial soaps at pH range 7.10 to 10.15, and found no role for the hydrogen ion concentration (i.e. pH) in skin irritation (page 199, left column). Bettley et al., "The Irritant Effect of Soap upon the Normal Skin," 72 Br. J. Dermatol. 67 (1960) tested complex soap and detergent solutions on normal human skin at pH range 5.9 to 10 and were "unable to discern any irritant effect due to alkalinity" (page 75, Conclusion). Guillot et al., "Evaluation of the Cutaneous-Irritation Potential of 56 Compounds," 20 Fd. Chem . Toxic. 563

(1982) studied the skin irritation of 56 chemicals used in cosmetic products in the rabbit skin. Guillot et al. found no consistent association between pH and skin irritation at pH range 2 to 10.8 (page 571, right column and page 572, left column). Oestreicher, "Detergents, Bath Preparations, and Other Skin Cleansers," 6 Clin. Dermatol. 29 (1988) teaches that "Based on present data, the pH may have little or no influence on the irritancy of soap and syndets" (page 33, left column). Singh et al., "Comparative Measurement of Irritant Properties of Toilet bar Soaps on Human Skin," 56 Indian J. Dermatol. Venereol. Leprol. 67 (1990) tested 10 commonly used toilet bar soaps for skin irritation on human skin and found no correlation between the pH of 5 % soap solutions and irritation. The tested pH range in this study was 10.11 to 10.66. Of special interest is a reference by Korting et al., "Influence of Skin Cleansing Preparation Acidity on Skin Surface Properties," 13 Int. J. Cosmet. Sci., 91 (1991) because in this study the skin irritation potential of liquid synthetic detergent preparations was investigated in a strictly controlled manner. The compositions of these preparations were identical, and the only difference was in pH (pH 5.5 vs.7.0 vs. 8.5). The skin irritation was measured by assessing skin roughness and transepidermal water loss (TEWL) over

a period of 59 days. Korting et al. found no difference in the skin roughness and TEWL between the tested preparations with pH values of 5.5, 7.0 and 8.5 (Figures 5-12). The authors conclude that "the skin irritancy of a cleansing preparation does not seem to be linked to its pH within the pH ranges tested". Cho et al., "Effect of the pH in Soaps on Skin Irritation," 4 Korean J. Invest. Dermatol, 124 (1997) teaches that "pH of the soaps is not major contributive factor of irritancy of the soaps" (page 124, Summary).

To the best knowledge of the applicants, only one peer-reviewed scientific reference in addition to Baranda et al. suggests that high pH of soaps would induce irritant effect. Lakshmi et al., "Irritancy Ranking of 31 Cleansers in the Indian Market in a 24-h Patch Test," 30 Int. J. Cosmet. Sci. 277 (2008) studied the skin irritation of 31 soaps and skin cleansers in healthy volunteers by scoring the erythema and scaling. Lakshmi et al. found that four products with pH 5-6 were less irritating than 27 products with pH 7-9 (page 281, Table II). Lakshmi et al. did not find any correlation between pH and irritation in the pH range 7 to 9. For example, Johnson baby soap with pH 7 was a stronger irritant than Pears with pH 8.

The Lakshmi et al. study has the same scientific flaw that Baranda et al.: the authors do not recognize that the soaps and skin cleansers are complex mixtures of ingredients that may cause skin irritation in the absence of high pH.

Instead of accepting Barenda et al. at face value, one of ordinary skill in the art would recognize the skin irritation exhibited by the soaps and skin cleansers tested by Baranda et al. may have been caused by one or more of their ingredients, such as surfactants, fragrances, preservatives, coloring agents, emulsifiers and plant extracts. See, for example, Paye., "Mechanisms of Skin Irritation by Surfactants and Anti-Irritants for Surfactant-Based Products," Handbook of Cosmetic Science and Technology 455 (3rd ed., Barel et al., eds., 2009), which states that surfactants are a major cause of skin irritation in many domestic products that contact skin, including body-cleansing liquids and solids (i.e., soaps and syndets). See also Oestreicher, which teaches the irritancy of a soap is a product of the surfactant properties (page 31, left column), and Van Der Valk et al., "Skin Irritancy of Surfactants As Assessed by Water Vapor Loss Measurements," 82 J. Invest. Dermatol. 291 (1984), which states that surfactants have different physiochemical properties

that affect skin reactions. Halvarsson et al., "Increasing Quality of Life by Improving the Quality of Skin in Patients with Atopic Dermatitis," 29 Int. J. Cosmet. Sci. 69 (2007) discusses adverse effects from cosmetics and states "neither foaming capacity nor pH is indicative of mildness. Differences in irritating capacity between cleansers with various pH appear more dependent on the combination of surfactants and their inherent irritating capacity than on pH of the products", Id. at 78.

Goossens et al., "Allergy and Hypoallergenic Products", Handbook of Cosmetic Science and Technology 455 (3rd ed., Barel et al., eds., 2009), describes factors which contribute to skin reactions to a cosmetic product, and lists the following as factors having harmful effects: fragrance ingredients, preservatives, antioxidants, active ingredients (such as natural extracts), excipients and emulsifiers, and coloring agents. Additionally, the concentration of the ingredients and their purity and impurity profile may have a role in skin reactions. Interestingly, Goossens et al. is completely silent on the role of pH in skin sensitivity to cosmetic products. See also Johansen, "Fragrance Contact Allergy," 4 Am. J. Clin. Dermatol. 789 (2003) which states fragrance ingredients (found in perfumes, deodorants, soaps and

other products) are one of the most frequent causes of contact allergic reactions (Abstract, second sentence), and Timm-Knudson at al., "Allergic Contact Dermatitis to Preservatives," 18 Dermatol. Nursing 130 (2006), which states that allergens which induce hand eczema commonly include preservatives and perfumes often found in lotions and soaps (Page 132, left column, lines 41-46).

In short, one of ordinary skill, aware of the teaching and data in the numerous references discussed above, would understand the skin irritation reported in Baranda et al. is related to the substances present in the complex mixtures of soaps and skin cleansers, and not to their pH.

Finally, the pH of the Stab et al. cream containing urocanic acid was 4.74, which pH is within "neutral zone" pH of the Group I soaps and skin cleansers of Baranda et al., where the skin irritation index was reported to be low. Accordingly, one of ordinary skill in the art would not be motivated by Baranda et al. to adjust the pH of the Stab et al. composition.

For the reasons discussed above, those skilled in the art would not be motivated by Wei et al. and/or Baranda et al. to adjust the 4.74 pH of the Stab et al. compositions to a pH range of 6.1 to 7.0. Reconsideration and withdrawal of the obviousness

rejection of claims 16, 19-22 and 28-30 over Stab et al. in view of Wei et al. are respectfully requested.

The 35 U.S.C. § 103(a) rejection of claims 16, 19-22 and 28-30 over Ben-Bassat et al., 6 Current Pharm. Design 933-942 (2000) in view of PCT Patent Publication WO 02/07520 to Wei et al. is also traversed. As discussed above, the claimed method includes administration of a pharmaceutical composition comprising a pharmaceutically acceptable agent or salt thereof capable of acidifying cell cytoplasm, wherein the pharmaceutically acceptable agent is an organic acid having a heterocyclic ring and a dissociation constant in the range 6.7 to 7.4, and wherein the agent is mixed with a carrier to adjust the pH of the composition to a pH range of 6.1 to 7.0. The claimed method specifies an effective amount of the pharmaceutically acceptable agent be administered in non-dissociated form to a person or animal.

The cited combination of references fails to raise a prima facie case of obviousness against the claimed method because (1) Ben-Bassat et al.'s compound AG18 is incapable of acidifying cell cytoplasm and (2) because one of ordinary skill in the art would not be motivated to adjust the pH of the Ben-Bassat et al. composition to a range of from 6.1 to 7.0.

The Rule 132 Declaration submitted with this Request demonstrates compound AG 18 is not capable of capable of acidifying cell cytoplasm. More specifically, the declaration reports careful experimental studies conducted with AG 18, which studies demonstrate that, in identical conditions where cis-urocanic acid is able to acidify the cell cytoplasm, AG 18 has no effect on intracellular pH. In this regard, Ben-Bassat et al. teaches that the inhibitory IC50 for AG 18 is in the range of 7-25 μM. The applicants used up to 14-fold higher concentrations of AG 18 and observed no cytosolic acidification after treatment with AG 18.

The data shown in the Declaration underline the fact that those skilled in the art cannot predict properties of a chemical compound by simply knowing its pKa value. Chemical and biochemical reactions, especially when taking place in the living, intact cell, are complex and unpredictable by nature. Simply knowing a compound's pKa value[5] does not mean the compound acts by acidifying

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[5]Because compound AG 18 fails to acidify cytosolic pH, the discussion about the pKa of AG 18 becomes irrelevant. Nevertheless, the inventors wish to comment as follows: The Patent Office cited a STN Registry Database which shows that AG 18 has a pKa value of 7.24. This pKa value was obtained from a publication [Gazit, 32 J. Medicinal Chem. 10, (1989)], which calculated the pKa value of AG 18 using Advanced Chemistry Development Software V8.19. Accordingly, the STN pKa value is also a theoretical estimate, which may be incorrect. Therefore, the calculated pKa value of AG

cell cytoplasm, or is capable of acidifying cell cytoplasm. In order to be able to acidify cell cytoplasm, the compound must fulfill several other criteria. First and most importantly, the molecule must accumulate in the cell cytosol, i.e., it must be able to move from the extracellular space into the cell interior and locate itself in the cytoplasm at high enough concentrations to have an impact on pH. Secondly, the molecule must be compatible with biological systems. Finally, the molecule in question must not interfere with other systems in the cell physiology, i.e., it should not be taken up or consumed by other biochemical events, such as receptor binding, enzyme activity, etc. that would prevent its accumulation in the cytoplasm. None of these essential properties can be predicted from the compound's pKa.

The Patent Office concedes Ben-Basset et al. fails to expressly disclose adjusting the pH of tyrosine kinase inhibitors such as compound AG 18 to a range of 6.1 to 7.0. One of ordinary skill, aware of the teaching and data in the numerous references discussed above, would ignore Wei et al.'s suggestion to use a "relatively neutral pH".

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18 provided by the applicants (i.e. pKa 8.14) may well be as correct as that given in the STN Registry database.

Reconsideration and withdrawal of the obviousness rejection of claims 16, 19-22 and 28-30 over Ben-Bassat et al. in view of Wei et al. are requested.

The provisional obvious-type double patenting rejection of claims 16, 19-22 and 28-30 over claims 13-18 and 20-23 of copending Application S.N. 11/408,056 in view of Granstein is traversed. The allegedly conflicting claims have not yet been allowed. Since this application is otherwise in condition for allowance, the provisional rejection should be withdrawn. A corresponding non-provisional rejection can then be made in the '056 application, if appropriate. Reconsideration and withdrawal of the provisional, obvious-type double patenting rejection of claims 16, 19-22 and 28-30 over claims 13-18 and 20-23 of the '056 application in view of Granstein are requested.

A Supplemental Information Disclosure Statement which submits the journal articles discussed herein, and cites references made of record in co-pending, commonly-assigned application S.N. 11/408,056, is attached.

It is believed this application is in condition for allowance. Reconsideration and withdrawal of all rejections of claims 16, 19-22 and 28-30, and issuance of a Notice of Allowance directed to

claims 16, 19-22 and 28, are earnestly requested. The Examiner is urged to telephone the undersigned should he believe any further action is required for allowance.

The RCE filing fee and extension of time fee are being paid electronically today. It is not believed any additional fee is required for entry and consideration of this Amendment, the Rule 132 Declaration and the Supplemental IDS. Nevertheless, the Commissioner is authorized to charge Deposit Account No. 50-1258 in the amount of any such required fee.

Respectfully submitted,

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Enclosures:
- Petition for Extension of Time
- Declaration Pursuant to 37 C.F.R. § 1.132
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